Abbreviations and Acronyms

ACT = activated clotting time
DS = diameter stenosis
LTO = late total occlusion
MI = myocardial infarction
MLD = minimal lumen diameter
PTCA = percutaneous transluminal coronary angioplasty
QCA = quantitative coronary angiographic
WRIST = Washington Radiation for In-Stent restenosis Trial

by the Institutional Review Board and the radiation safety committee at the Washington Hospital Center. All patients signed consent forms before enrollment and completed at least six months of clinical and angiographic follow-up.

The description of trials, the isotope, and the dose are displayed in Table 1. The protocols had similar inclusion criteria including in-stent restenosis with a diameter stenosis (DS) >50%, in vessels 2.5 to 5.0 mm in diameter, a lesion length up to <80 mm, and successful primary intervention by balloon, ablation (laser or rotational atherectomy), restenting, or the combination with a <30% residual DS without complications. The main exclusion criteria were patients with acute myocardial infarction (MI) <72 hours previously, a left ventricular ejection fraction <20%, prior irradiation treatment to the chest, evidence of thrombus by angiogram, and multiple lesions in the same vessels.

Typically, focal lesions (<10 mm in length) were approached with balloon dilation, and diffuse lesions (≥10 mm in length) underwent ablation using excimer laser angioplasty or rotational atherectomy. Restenting was performed in 41% of patients when necessary to optimize the primary angiographic results, to cover the entire lesion length (especially when the in-stent restenosis process extended beyond the length of the stent) or to treat edge dissections. In preparation for the radiation treatment the activated clotting time (ACT) was monitored and adjusted with heparin to exceeded 300. The source was delivered per protocol and left in place for a sufficient time to deliver the assigned dose. Cinefluoroscopy was used to verify catheter and source position.

Following radiation procedure, a final angiogram was performed and further balloon dilation or stent implantation was performed if the angiographic result had deteriorated significantly (>30% DS). The femoral sheaths were removed at the day of the procedure and patients received routine after-angioplasty care including ticlopidine 250 mg twice daily or clopidogrel 75 mg daily for one month and aspirin 325 mg daily. Gamma-1 patients who underwent restenting were instructed to continued ticlopidine for two months.

All patients completed clinical and angiographic follow-up at six months after enrollment. Quantitative coronary angiographic (QCA) analysis was performed using automated edge-detection algorithm. Selected end-diastolic cineframes were optically magnified (2.4:1) and digitized using a cine-video converter. Using the contrast filled catheter as the calibration standard, minimal lumen diameter (MLD), reference diameter, and percent diameter stenosis (DS) pre- and postintervention were measured. For the purpose of the current analysis, subacute thrombosis was defined as angiographically documented total occlusion ≤30 days; and LTO was defined as angiographically documented total occlusion >30 days' postintervention. The LTO was applied for patients who had patent artery at six months' follow-up and presented with total occlusion of the same site at a later time.

The time to LTO and the relevant clinical event associated with LTO were recorded and adjudicated. Several approaches were used to treat the LTOs including thrombolytics (5 patients), thrombectory (Angioget, Possis Medical, Minneapolis, Minnesota), PTCA (percutaneous transluminal coronary angioplasty) (14 patients), coronary artery bypass surgery (7 patients), and conservative medical therapy (7 patients); these treatment choices were not mutually exclusive.

Statistical analysis. Data were recorded prospectively and forwarded to the data-coordinating center. The results are expressed as mean ± 1 SD. Continuous variables were compared using unpaired, two-tailed Student *t* test. Categorical values were compared using chi-square or the Fisher exact test. P values <0.05 were considered statistically significant. Multivariate logistic regression analysis to determine the predictors of late thrombosis included demographic, morphological and

Table 1. Rate of Late Total Occlusion by Studies, Emitters, and Doses

Study	Emitter	Dose (Gy)	Late Total Occlusion Rate	
			Treated	Control
WRIST	Ir-192	15 at 2 mm	10/104 (9.6%)	2/65 (3.1%)
GAMMA-1	Ir-192	8–30 by IVUS	3/20 (15%)	0/20 (0%)
ARTISTIC	Ir-192	15 at 2 mm	2/24 (8.3%)	0/8 (0%)
SVG WRIST	Ir-192	15 at 2 mm	1/27 (3.7%)	0/27 (0%)
LONG WRIST	Ir-192	15 at 2 mm	4/45 (8.8%)	0/45 (0%)
High-dose WRIST	Ir-192	15 at 2.4 mm	2/29 (6.9%)	*
BETA WRIST	Y-90	20.6 at 1 mm	4/49 (8.1%)	*
PREVENT	P-32	20–24 at 1 mm	2/10 (20.0%)	0/5 (0%)
TOTAL	All	Any	28/308 (9.1%)	2/165 (1.2%)

*Registries in which all patients received radiation.

Table 2. Clinical, Procedural, and Angiographic Findings in 28 Patients Who Received Brachytherapy for In-stent Restenosis and Who Presented With Late Total Occlusion

Demographics	
Age (yrs)	58.0 ± 11.4
Gender (male)	67.8
Number of in-stent restenosis episodes	2.3 ± 1.5
Angiographic findings preintervention	
Reference (mm)	2.44 ± 0.34
Minimal luminal diameter (mm)	0.76 ± 0.37
Diameter stenosis (%)	76 ± 15
Device used to treat in-stent restenosis*	
Balloon	8 (28.6%)
Rotational atherectomy	12 (42.8%)
Excimer laser angioplasty	8 (28.6%)
Restenting	23 (82.1%)
Angiographic findings postintervention	
Minimal luminal diameter (mm)	2.05 ± 0.42
Diameter stenosis (%)	26 ± 9
Clinical presentation of late total occlusion	
Time to late total occlusion (months)	5.4 ± 3.2
Acute MI	12 (42.8%)
Recent onset unstable angina	14 (50.0%)
Asymptomatic	2 (7.2%)

*Not mutually exclusive.

clinical variables. Logistic regression is widely used to fit models for binary or ordinal, multicategorical variables. We entered all clinically relevant variables in the model, and then backward selection method was used to find predictors of the outcome. We used a level of 0.05 as a cut-off point to let the predictors stay in the model.

RESULTS

Of the 473 patients entered into the various trials, 308 patients were treated with active radiation and 165 were treated with placebo. *Subacute* thrombosis occurred in three (0.9%) patients treated with radiation and in none of the placebo-treated patients. *Late total occlusion* occurred in 28 patients treated with radiation (9.1%), but in only 2 placebo patients (1.2%, $p < 0.0001$). Late late total occlusion occurred in two patients (0.6%) treated with radiation and none of the placebo patients. The rate of LTO did not vary significantly across protocols, emitters, and dosage. The clinical, angiographic, and procedural details of the 28 patients who received radiation to treat in-stent restenosis and who presented with LTOs are shown in Table 2. The mean time to LTO was 5.5 ± 3.1 months, with the majority of the 24 patients presenting between two and seven months. Late LTO occurred in two patients at 12 and 18 months despite absence of pathology on a six-month angiographic follow-up. The LTO was associated with acute MI in 12 (43%) of the patients and unstable angina in 14 (50%) patients; only 2 (7%) LTO patients were asymptomatic; in these patients total occlusions were found at routine six-month follow-up. The LTO from the irradiated group was treated: medically, 9 patients; repeat angioplasty, 14 patients; bypass surgery, 5 patients. There were three deaths among the patients who presented with LTO, one death from the medically treated group, one postbypass surgery, and one following angioplasty. The two patients with total occlusion from the placebo group were crossed over to radiation therapy and presented with patent artery at six months.

Restenting as part of the treatment of in-stent restenosis was performed in 230 of 473 (48.6%) patients. Importantly, 22 of the 28 irradiated patients (79%) who subsequently presented with LTO had a new stent placed during the treatment of in-stent restenosis. The LTO rate among patients who received stents and radiation was 14.6%. The rate of LTO in the patients who were treated with radiation, but no new stenting, was 6 of 157 (3.8%).

Multivariate logistic regression analysis was performed for the patients in the various WRIST studies. We specifically entered the following variables into the model: gender, diabetes, lesion length, reference vessel diameter, lesion length, final lumen diameter, beta radiation gamma radiation, and additional stenting. New stenting (odds ratio [OR] = 2.55, 95% confidence interval [CI] = 1.0–5.1, p = 0.04), and long lesions (OR = 1.15, CI = 1.0–1.2, p = 0.04) were found to be the predictors for late thrombosis.

DISCUSSION

In the current study we report a high rate of LTOs in patients undergoing radiation therapy to prevent recurrent in-stent restenosis. Although some of these LTOs may be the result of excessive tissue proliferation and exaggerated in-stent restenosis, the clinical and angiographic features suggest that the main etiology for LTO for this cohort is thrombus formation. Late thrombosis following coronary intervention and vascular brachytherapy is a new phenomenon. Because late thrombosis is rarely seen following conventional intervention, the cases of late thrombosis in the current study should be attributed to the use of radiation therapy.

Mechanisms. We have previously reported a correlation between the radiation dose and the thrombosis rate in the porcine model (18). Our findings suggested that healing response in irradiated arteries is delayed and that this delay may promote thrombus formation—especially in stented arteries with impaired re-endothelialization. In the current study, LTO was manifest as late closure and was found irrespective to the type of the radiation (beta versus gamma) or the prescribed dose to the vessel wall or the adventitia. Salame et al. (19) observed platelet recruitment at the irradiated injured site in porcine coronaries at 28 days. Previous studies on the vascular effects of external beam radiation have suggested that increased thrombosis is an adverse late healing effect (10,11). Furthermore, thrombi present in irradiated arteries tend to be acellular, with an absence of macrophages and lymphocytes thought to be involved in the repair mechanism. Decreased numbers or impaired function of macrophages may prolong the residence of the thrombus and its components (platelets and fibrin) at the injured segment and may delay its organization. Our animal

studies showed that thrombosis is related more to the total dose at the adventitia rather than to the luminal surface (18). Recent studies examining human carotid arteries that were exposed to external radiation have demonstrated impaired endothelium with reduction of nitric oxide production, which can potentially result in thrombosis (20).

Predictors of late thrombosis. In the current study, late thrombosis occurred mainly in patients who underwent new stent implantation at the time of brachytherapy. Conversely, the late thrombosis rate in patients who did not receive a new stent at the time of irradiation was similar to the nonirradiated group. Restenting an in-stent restenosis lesion has been advocated as one approach to this clinical problem. While it achieves the largest acute lumen dimensions, the long-term recurrence rate may be similar to other nonbrachytherapy techniques.

There are a number of potential explanations for late thrombosis in the setting of new stent implantation. First, small dissections can occur at the stent edges of newly implanted stents. Radiation may delay the healing of these edge dissections, which may remain thrombogenic. In a recent study using beta radiation, it was found that 7 of 16 (45%) dissections in unstented arteries remained unhealed at six-month follow-up (21). Second, incomplete, delayed, or impaired re-endothelialization may contribute to the initiation of a thrombus. Although the majority (26/28) of late thromboses occurred between two and seven months following irradiation, two patients had documented patency at six months and presented with "late late total occlusion" at 12, and 18 months. The "late LTOs" may be related to regression or erosion of tissue outside the stent. This may leave the stent unopposed to the vessel wall and serve as a nidus for thrombosis.

Conclusions. Our study clearly demonstrates a new complication of intracoronary radiation for patients with in-stent restenosis—*late total occlusion*. This phenomenon is more pronounced after restenting, but not after radiation and no new stenting.

These findings suggest that patients treated with stenting and radiation should be placed on prolonged antiplatelet therapy; we suggest a duration of at least six months. However, it is possible that prolonged antiplatelet therapy will only delay late thrombosis. If this occurs, increasing the rate of "late LTO," antiplatelet therapy will be required for longer than six months or other agents that may enhance the healing response and the re-endothelialization of new stents placed in irradiated arteries. Further, restenting should be avoided unless absolutely necessary, and the use of heparin-coated stents may be beneficial.

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Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis

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Lack of Effect of Lovastatin on Restenosis after Coronary Angioplasty

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ABSTRACT

Background Experimental and clinical observations suggest that lowering serum lipid levels may reduce the risk of restenosis after coronary angioplasty. We report the results of a prospective, randomized, double-blind trial evaluating whether lowering lipid levels with lovastatin can prevent or delay restenosis after angioplasty.

Methods Seven to 10 days before angioplasty, we randomly assigned eligible patients to receive lovastatin (40 mg orally twice daily) or placebo. Patients who underwent successful, complication-free, first-time angioplasty of a native vessel (the index lesion) continued to receive therapy for six months, when a second coronary angiogram was obtained. The primary end point was the extent of restenosis of the index lesion, as assessed by quantitative coronary arteriography. Of 404 patients randomly assigned to study groups, 384 underwent angioplasty; 354 of the procedures were successful, and 321 patients underwent angiographic restudy at six months.

Results At base line, the patients in the lovastatin group (n = 203) and the placebo group (n = 201) were similar with respect to demographic clinical, angiographic, and laboratory characteristics. At base line the mean (±SD) degree of stenosis, expressed as a percentage of the diameter of the vessel, was 64 ±11 percent in the lovastatin group, as compared with 63

±11 percent in the placebo group (P = 0.22). Despite a 42 percent reduction in the serum level of low-density lipoprotein cholesterol in the lovastatin group, after six months of treatment the amount of stenosis seen in the second angiogram was 46 ±20 percent in the placebo group, as compared with 44 ±21 percent in the lovastatin group (P = 0.50). Similarly, there were no significant differences in minimal luminal diameter or other measures of restenosis. A trend was noted toward more myocardial infarctions in the lovastatin group, as a result of acute vessel closure or restenosis at the site of angioplasty, but there were no other important differences between the two groups in the frequency of fatal or nonfatal events at six months.

Conclusions Treatment with high-dose lovastatin initiated before coronary angioplasty does not prevent or delay the process of restenosis in the first six months after the procedure.

Although the use of percutaneous transluminal coronary angioplasty has increased dramatically,[1] restenosis remains an important limitation of the procedure. Several pathophysiologic characteristics suggest similarities between the processes of restenosis and atherosclerosis[2]. Furthermore, recent experimental and clinical data suggest that lowering serum lipid levels with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors such as lovastatin may prevent or delay the process of restenosis[3,4,5]. The purpose of the Lovastatin Restenosis Trial was to determine whether aggressive therapy to lower lipid levels (40 mg of lovastatin twice daily for 6 months), initiated 7 to 10 days before angioplasty, would decrease the extent or the frequency of restenosis, as assessed by quantitative coronary arteriography after the procedure.

Methods

Patients and Study Design

From January 1991 through October 1992, we enrolled 404 patients in this prospective, randomized, double-blind, placebo-controlled trial[6]. Patients in whom angioplasty was unsuccessful or who had acute complications were excluded from the analysis of angiographic end points. The protocol was approved by the institutional review board at each participating institution. Complications and clinical outcomes were reviewed by an independent data and safety monitoring board.

Of 5483 patients screened at the 11 centers, 510 (9.3 percent) were eligible, and 404 (79 percent of the eligible patients) were randomly assigned to study groups. The chief reasons for exclusion were a prior angioplasty (in 969 patients), inability to wait seven days for angioplasty (1679), the absence of a suitable lesion (330), a recent myocardial infarction (1004), use of cholesterol-lowering medications (318), and a total cholesterol level below 160 mg per deciliter (4.1 mmol per liter) or above 300 mg per deciliter (7.8 mmol per liter) (146). The eligible patients had at least one area of stenosis of 50 to 99 percent in a native vessel over 1.5 mm in diameter that supplied viable myocardium, and they were estimated to have a 90 percent chance of successful angioplasty. The index lesion for the analysis of primary end points was the lesion in the first successfully dilated native vessel, with success defined as residual stenosis of less than 50 percent and an increase of 20 percent or more from the base-line

diameter of the vessel.

Eligible patients who had given informed consent were randomly assigned to receive either lovastatin (40 mg orally twice daily) or placebo. The patients returned 7 to 10 days after randomization for angioplasty; if the first site was successfully dilated and the procedure was not complicated by myocardial infarction, the need for coronary surgery, or death, the study medication was continued in a blinded fashion for 6 months, after which angiography was repeated and stress thallium scintigraphy was performed. Fasting serum lipids, aspartate and alanine aminotransferase, and creatine kinase were measured at base line and 4, 12, 18, and 26 weeks after angioplasty[6]. Instructions to the patient on compliance with the Step 1 American Heart Association diet and the dosage of study medication were reinforced at each visit.

Lipid Measurements

All lipid measurements and other chemical analyses were performed at a core laboratory, which was certified by the Lipid Standardization Program of the Centers for Disease Control and Prevention, by technicians blinded to the clinical and angiographic data. A detailed safety algorithm was developed for the adjustment of doses or discontinuation of the study medications[6].

Angiographic Methods

Catheterization and angioplasty were performed according to standard techniques. Arteriograms were obtained before and immediately after angioplasty and at the six-month examination, in the same projections, and were included in the quantitative analysis of coronary arteriography. These analyses were performed according to a validated method[7]. Repeated measurements of 52 stenoses by two independent observers were compared (mean [±SD] degrees of stenosis measured, 55 ±18 percent and 56 ±19 percent of the vessel diameter; P = 0.64). The 95 percent confidence interval for the difference was -1.64 to 1.02 percent. The single end-diastolic frames that best defined each dilated stenosis in two near-orthogonal views were identified. These frames were magnified optically, digitized, and stored as images in a computer. All paired images were then evaluated side by side, to facilitate consistent analysis. Edges were determined with computer-assisted visual edge detection. The mean values for the two views and the two observers' judgments of the degree of stenosis and the minimal diameter of the lumen and a normal segment (in millimeters) were determined. Morphometric analyses of the characteristics of the lesions were performed as previously described[8].

Exercise Electrocardiography and Thallium Scintigraphy

Patients exercised according to the Bruce or Naughton protocol to 85 to 100 percent of the maximal predicted heart rate, at which time thallium was injected. Imaging began after recovery. Pharmacologic stress, produced by the infusion of 0.142 mg of dipyridamole per kilogram of body weight per minute for five minutes, was used in patients who were unable to exercise.

End Points

The primary end point in the study was the degree of stenosis, expressed as a percentage of the diameter of the vessel at the site of the index lesion. Other angiographic end points included the minimal luminal diameter, the proportion of patients in each group with stenosis of 50 percent or more on the second angiogram or loss of 50 percent or more of the diameter gained immediately after angioplasty (late loss), and the ratio of late loss to initial gain for the index segment and for all dilated segments. End points assessed noninvasively included the characteristics of the exercise electrocardiogram and the results of thallium scintigraphy. Clinical end points included congestive heart failure, recurrent angina, the need for additional revascularization procedures, myocardial infarction, stroke, and death. Myocardial infarctions were diagnosed by the appearance of new Q waves, chest pain, or both plus increases in creatine kinase levels to more than twice base-line levels with 5 percent MB subunit. All clinical cardiovascular events were reviewed by the mortality and morbidity committee.

Data Collection and Statistical Analysis

All data were recorded on standardized forms and entered into the data base. Adverse events were reported promptly to the sponsor. The data are expressed as proportions or as means ±SD. Differences between the groups in categorical variables were analyzed by Fisher's exact test, and continuous variables by Student's two-sample t-test. For all statistical testing, we used two-tailed P values. The study had a power of 80 percent to detect differences of 7 percent between the groups and a power of 90 percent to detect differences of 8 percent in the degree of stenosis, based on a sample of 340 patients evenly divided between two groups, an alpha level of 0.05, a two-sided t-test, and a standard deviation of 22 percent for the percentage of stenosis at restudy.

Results

A total of 203 patients were randomly assigned to receive lovastatin, and 201 were assigned to receive placebo; 191 in the lovastatin group and 193 in the placebo group underwent angioplasty 8.7 ±3.9 days later. Angioplasty was successful in 90 percent of the lovastatin group and 94 percent of the placebo group (P = 0.12). Among the patients in whom the procedure was successful, angiography was repeated at six months in 91 percent: 160 in the lovastatin group and 161 in the placebo group (P = 0.14).

Base-Line Characteristics

The two groups were similar in terms of base-line characteristics (Table 1). The patients' mean age was 62 years; 28 percent were women. Systemic arterial hypertension was present in approximately 50 percent, about 11 percent had diabetes mellitus, about 25 percent had a history of myocardial infarction, less than 10 percent had previously undergone cardiac surgery, and just over 50 percent had grade III or IV angina. Congestive heart failure was unusual. The proportions who used antianginal medications and aspirin were similar in the two groups (84 percent of the lovastatin group and 81 percent of the placebo group). The mean ejection fraction was 60 percent in both groups, and the majority had single-vessel disease. In 2.6 percent of the cases the procedure was stopped before any dilatation was attempted because of a decision by the operator or inability to cross the lesion. Overall, one site was dilated in 74 percent of patients, and two or more sites in 26 percent. The location of the index lesion varied slightly

between the groups, with no significant difference in the proportion in the left anterior descending artery. There were trends toward more branch-point lesions in the placebo group (28 percent, vs. 20 percent in the lovastatin group) and more atherectomies (2.5 percent, vs. 0 percent in the lovastatin group); otherwise there were no notable morphologic or procedural differences between the two groups of patients.

View this table: **Table 1.** Base-Line Characteristics of the Patients, According to Study Group.
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Lipid Levels

At base line the mean cholesterol level was 205 ±32 mg per deciliter (5.3 ±0.8 mmol per liter) in the lovastatin group and 201 ±33 mg per deciliter (5.2 ±0.8 mmol per liter) in the placebo group. The level of low-density lipoprotein (LDL) cholesterol was 130 ±30 mg per deciliter (3.4 ±0.8 mmol per liter) in the lovastatin group and 126 ±30 mg per deciliter (3.3 ±0.8 mmol per liter) in the placebo group; that of high-density lipoprotein (HDL) cholesterol was 38 ±14 mg per deciliter (1.0 ±0.4 mmol per liter) in the lovastatin group and 38 ±11 mg per deciliter (1.0 ±0.3 mmol per liter) in the placebo group. Among the patients who received lovastatin, LDL cholesterol fell by 34 percent to 86 ±27 mg per deciliter (2.2 ±0.7 mmol per liter) at one week and by a total of 42 percent to 75 ±22 mg per deciliter (1.9 ±0.6 mmol per liter) at one month, but the LDL cholesterol level was unchanged in the placebo group ($P<0.001$). By one month, the HDL cholesterol level had risen slightly to 42 ±13 mg per deciliter (1.1 ±0.3 mmol per liter) in the lovastatin group and was unchanged in the placebo group. The changes in lipid levels largely persisted; at six months the LDL cholesterol level was 88 ±32 mg per deciliter (2.3 ±0.8 mmol per liter) in the lovastatin group and 131 ±33 mg per deciliter (3.4 ±0.8 mmol per liter) in the placebo group ($P<0.001$). The serum level of aspartate aminotransferase or alanine aminotransferase was three or more times the upper limit of normal in 3 of 172 patients in the lovastatin group (1.7 percent), as compared with 1 of 173 in the placebo group (0.6 percent, $P = 0.37$). Three of 172 patients given lovastatin (1.7 percent) and none in the placebo group had creatine kinase levels 10 or more times the upper limit of normal without myocardial infarction ($P = 0.12$). Lovastatin treatment was stopped in one patient who had elevated creatine kinase levels that persisted after dose reduction, with a return to base-line levels within two weeks. At the time of follow-up angiography, the patients in each group were taking 1.9 ±0.6 pills per day, and no patients receiving placebo were taking medication to lower serum lipid levels.

Clinical Outcomes in the Hospital and at Six Months

Angioplasty was successful in over 90 percent of both groups (Table 2). Intimal tears occurred in 11.0 percent of the patients assigned to lovastatin and 14.5 percent of those in the placebo group; dissections were unusual. Acute Q-wave myocardial infarctions occurred in about 1 percent of the patients, and there was one death (in the lovastatin group) in the hospital. Clinical success was achieved in 90.1 percent of the lovastatin group and 94.3 percent of the placebo group.

View this table: [in this window] [in a new window] **Table 2.** Clinical Characteristics and Outcomes during the Initial Hospitalization and at the Six-Month Evaluation, According to Study Group.

Most of the patients who completed the trial were asymptomatic at six months of follow-up, and there was no significant difference in the frequency of angina, congestive failure, or use of cardiac medications between the groups. There were a total of three deaths in the lovastatin group and one in the placebo group ($P = 0.62$). There was a trend toward more myocardial infarctions (both Q-wave and non-Q-wave) in the lovastatin group. Of the 19 myocardial infarctions, 1 (in a patient in the lovastatin group) occurred before the index lesion could be dilated. Twelve myocardial infarctions occurred during the initial hospitalization (eight in the lovastatin group and four in the placebo group), with documented acute closure in eight (six in the lovastatin group and two in the placebo group). One myocardial infarction occurred three days after angioplasty at a remote site in a patient in the lovastatin group. Late myocardial infarctions occurred at the original angioplasty sites in four patients (three in the lovastatin group and one in the placebo group); one occurred after repeated dilation in a patient receiving lovastatin. In one patient who died (also a patient receiving lovastatin), the site of the myocardial infarction could not be confirmed. There was no significant difference between the groups in the need for additional revascularization procedures or the incidence of stroke. The number of patients who were free of all events, including myocardial infarction, stroke, coronary surgery, repeated angioplasty, and death, did not differ significantly between the groups.

Angiographic Assessment

The results of angiographic assessment of the site of the index lesion are presented in Table 3. The normal zone did not change in diameter and did not vary between the groups at any time. There were no significant differences at base line in the minimal luminal diameter or the percentage of stenosis. Though there was a slight trend toward a larger minimal luminal diameter and a lower percentage of stenosis in the placebo group after angioplasty, there was no difference between the groups in the change in these measures from values obtained at base line to those obtained after the procedures (short-term gain). At angiographic restudy, the minimal luminal diameter was 1.4 ±0.6 mm in the lovastatin group and 1.5 ±0.6 mm in the placebo group ($P = 0.30$), and there was stenosis of 46 ±20 percent in the lovastatin group and 44 ±21 percent in the placebo group ($P = 0.50$). There were no differences between the groups in the change in degree of stenosis or the minimal luminal diameter from the values measured before angioplasty to those obtained at follow-up (net gain) or from those measured immediately after angioplasty to those obtained at follow-up (late loss) (Table 3). The 95 percent confidence intervals for the difference in the percentage of stenosis between the placebo and lovastatin groups when restudied angiographically were -6.15 to 3.01 percent for the degree of stenosis and -0.063 to 0.20 mm for the minimal luminal diameter. The 95 percent confidence intervals for the difference in late loss were -4.18 to 5.05 percent for degree of stenosis and -0.15 to 0.11 mm for minimal luminal diameter. The late-loss index (late loss divided by short-term gain) did not vary significantly between the groups. When we defined restenosis as stenosis of 50 percent or more of the vessel diameter, the rate of restenosis was 39 percent in the lovastatin group and 42 percent in the placebo group ($P = 0.65$). There was loss of 50

percent or more of the short-term gain in 42 percent of the patients in the lovastatin group and 48 percent of those in the placebo group (P = 0.31). Total occlusion was present at six months in four patients who received lovastatin (2.5 percent), as compared with three (1.9 percent) who received placebo (P = 0.72). These results were confirmed for the secondary end points at all dilated lesions (data not shown).

View this table: **Table 3.** Angiographic Results at the Index Lesion, According to Study Group.
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Figure 1 shows the cumulative distribution curves for the degree of stenosis at the index lesion before angioplasty, after angioplasty, and at the second angiography at six months. The curves move from the right before angioplasty to the left after angioplasty, indicating short-term gain. At restudy, the curves move back to the right, reflecting late loss. The curves for the two groups are essentially superimposed at each angiographic evaluation. Figure 2 shows the cumulative distribution curves for late loss. The curves for the two groups are essentially superimposed. Curves for the minimal luminal diameter at the site of the index lesion and for the degree of stenosis and the minimal luminal diameter at all dilated sites (data not shown) were similarly superimposed.

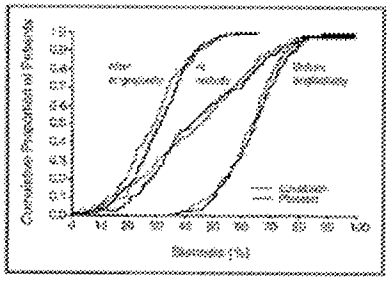

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Figure 1. Cumulative Distribution Curve for the Degree of Stenosis at the Index Lesion before Angioplasty, after Angioplasty, and at Angiographic Restudy at Six Months, According to Treatment Group.

The degree of stenosis is expressed as a percentage of the vessel diameter.

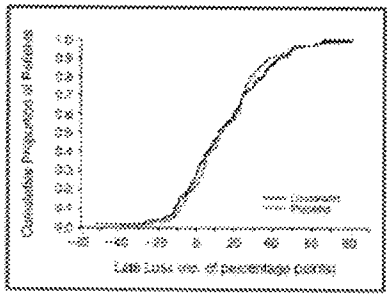

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Figure 2. Cumulative Distribution Curve for the Change in the Degree of Stenosis at the Index Lesion from the Value Measured Immediately after Angioplasty to the Value Obtained on Angiographic Restudy (Late Loss), According to Treatment Group.

Late loss is calculated as the difference in the two values, each of which expresses the degree of stenosis as a percentage of the diameter of the vessel.

There was no discernible relation between the LDL or the HDL cholesterol level one month after angioplasty and the change in the degree of stenosis from the value measured before angioplasty to that measured at the six-month restudy (late loss) (correlation coefficients, -0.04 and 0.01, respectively). Lipid values one month after the procedure were chosen to reflect the peak treatment effect, active cellular proliferation, and the process of restenosis.

Results of Noninvasive Testing

In each group, 140 patients underwent exercise or dipyridamole stress tests (Table 4). There was no significant difference between the groups in exercise time, peak blood pressure, peak heart rate, or rate-pressure product (the heart rate times the systolic blood pressure). There was a trend toward a greater peak ST-segment deviation in the lovastatin group; the ST segment was depressed at least 1 mm in 39 percent of the lovastatin group and 30 percent of the placebo group ($P = 0.16$). There was no significant difference in the incidence of angina during the test. Defects, either fixed or reversible, were noted on thallium scanning in 46 percent of the patients who received lovastatin and 49 percent of those given placebo ($P = 0.62$).

View this table: [in this window] [in a new window] **Table 4.** Results of Exercise Testing and Thallium Scintigraphy, According to Study Group.

Discussion

These data provide compelling evidence, based on multiple continuous and categorical measures, that substantial reductions in LDL cholesterol levels do not prevent or reduce the frequency or degree of restenosis after coronary angioplasty. Lovastatin markedly lowered LDL cholesterol levels and was well tolerated; only one patient stopped taking the drug because of an adverse effect. Although there was a trend toward more myocardial infarctions in the lovastatin group, there were few Q-wave myocardial infarctions overall, and 16 of the 19 infarctions that did occur were related to acute vessel closure or restenosis. There was only one confirmed myocardial infarction at a site not dilated during angioplasty; this result is consistent with those of the large, multicenter Expanded Clinical Evaluation of Lovastatin study[9].

The incidence of myocardial infarction in the lovastatin group was similar to the rates noted in the angioplasty registry of the National Heart, Lung, and Blood Institute (incidence, 4.7 percent soon after the procedure and 7.2 percent at one year) and two large, multicenter angioplasty trials, whereas the incidence of myocardial infarction in the placebo group was lower[10,11,12]. There was no difference between groups in the composite end point of myocardial infarction, stroke, coronary surgery, repeated angioplasty, or death. Although more patients in the lovastatin group had ST-segment abnormalities on their exercise electrocardiograms at follow-up, no difference was noted in the thallium-imaging studies.

The design of the trial -- which featured aggressive measures to lower lipid levels and a pretreatment period before balloon angioplasty, as well as careful quantitative measurement of coronary stenoses -- provided the highest probability that we would be able to detect an effect of treatment if one existed. Lovastatin lacked therapeutic efficacy even though there was a high rate of restenosis, consistent with the rates in many other studies[4,5]. In addition, no treatment effect was observed even in patients with elevated LDL cholesterol levels, and there was no relation between the LDL cholesterol level and the degree of stenosis or the minimal luminal diameter at six months after angioplasty.

Data from previous studies of the relation between serum lipids and restenosis conflict,[13,14,15,16,17,18] but these studies were not designed to evaluate that relation prospectively. Recent preclinical and clinical studies have increased interest in this relation[3,4,5]. Elevated LDL cholesterol levels increase platelet and red-cell aggregability,[19,20] and thrombosis is believed to have a decisive role in the process of restenosis[21]. Lowering LDL cholesterol levels decreases rates of restenosis in the rat-carotid model,[3] whereas treatment with lovastatin decreases the progression of disease in the rabbit-iliac model[4] independently of an effect on LDL cholesterol. In contrast, in the overstretched-swine-coronary model, no relation between either LDL cholesterol or lovastatin and restenosis was observed[22]. An attempt was made to resolve these conflicts with a prospective clinical study in which 157 patients were treated with lovastatin or conventional care[5]. Although that study was neither randomized nor blinded and the angiographic follow-up was incomplete, the rate of restenosis was 12 percent with lovastatin and 44 percent with conventional care. Our trial did not confirm these preliminary data, and the prospective, randomized, placebo-controlled, double-blind design of our multicenter study, with a larger sample, a higher dose of drug, a pretreatment phase, more complete angiographic follow-up, and careful end-point analysis, makes it unlikely that aggressive lowering of LDL cholesterol levels reduces the risk of restenosis.

Several angiographic trials have found decreased progression of disease and even some regression of atherosclerosis when lipid levels are lowered,[23,24,25,26,27,28,29,30] and these findings were correlated in some of these trials with a decreased frequency of cardiovascular events[24,25,26]. In none of these trials did lowering lipid levels result in an increased incidence of myocardial infarction or other clinical events. Furthermore, angiographic evidence of the progression of disease is related to future cardiovascular events[31,32]. The contrasting effects of lower lipid levels on atherosclerosis and restenosis make it unlikely that restenosis can be viewed simply as an acceleration of atherosclerosis in response to a severe mechanical injury.

Most interventions have failed to reduce the frequency or degree of restenosis after angioplasty. The few trials with positive results, such as those using fish oil, are counterbalanced by negative studies[33,34,35,36,37,38,39]. Similarly, conflicting results have been noted for the somatostatin analogue angiopeptin[40]. A better understanding of the pathophysiology of restenosis is needed, as are experimental models that more closely approximate restenosis in humans. The high probability of restenosis will continue to be a major limitation on the value of angioplasty until the vascular biology is understood.

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Source Information

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Appendix

The following investigators and institutions participated in the Lovastatin Restenosis Trial: Clinical Coordinating Center: W.S. Weintraub, C.L. Brown III, S.B. King III, R.W. Alexander, C.L. Cohen-Bernstein, D. Owen, and P. Schumacher; Merck Research Laboratories: S.J. Boccuzzi, Y.B. Mitchel, L.J. Hirsch, M.R. Melino, O.P. Beattie, D. Gudel, D. Plotkin, A. Tate, R. Zupkis, and D. Shapiro; Data and Safety Monitoring Board: W.D. Hall (chairman), M. Kutner, N. Watts, and R. Schlant; Biostatistical Coordinating Center: A.S. Kosinski, Y. Shen, F. Hicks, D. Canup, and P. Per-Lee; Lipid Core Laboratory: D.C. Robbins, A. Le, J. Howard, B. Howard, W.V. Brown, and X. Li; Angiographic Core Laboratory: J.L. Klein, C. Treasure, and S. Gatlin; Electrocardiographic Core Laboratory: J.W. Hurst and D. Schroeder; Mortality and Morbidity Committee: D. Harrison (chairman), P. Delafontaine, M. Runge, and D. Schroeder; Thallium Advisory Board: N. Alazraki and A. Taylor; Emory University Hospitals, Atlanta: C.L. Brown III, W.S. Weintraub, S.B. King III, R.W. Alexander, J.S. Douglas, Jr., S. Kim, A. Thornton, C.L. Cohen-Bernstein, S. Haynes, J. Webster, J. Merlino, D.C. Morris, H.A. Liberman, C. Treasure, J.L. Klein, and N. Alazraki; Florida Hospital, Orlando: R. Ivanhoe, C. Weaver, C. Curry, W. Willis, and D. Ross; Charlotte Memorial Hospital, Charlotte, N.C.: J.C. Cedarholm, R.M. Bersin, C.M. Elliot, R.H. Haber, G.J. Kowalchuk, C.A. Simonton, B.H. Wilson, S.H. Zimmern, B. Porter, and T. Tucker; Saint Thomas Hospital, Nashville: M. Crenshaw, D. Hall, H. Walpole, M. Glazer, J. Thompson, E. Spitler, and A. Churchwell; Baylor Hospital, Dallas: S.J. DeMaio, R.L. Rosenthal, J.R. Schumacher, J.M. Grodin, S.B. Johnston, J.O. Franklin, B.M. Leonard, F. Rosenberg, and A. Raich; Medical Center of Delaware, Wilmington: M.E. Stillabower, E.M. Goldenberg, A.J. Doorey, J. West,

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